toward the soluble APRIL polypeptide, or fragment thereof, as described on page 17, lines 16-29.

Applicant has also added claims 46-49 drawn to methods for identifying an agent capable of suppressing the growth of a cell culture. Claims 46 and 49 are supported by the disclosures on page 26, line 24 to page 27, line 8; Example 2, pages 32-34; and p. 30, line 30 to page 31, line 3. Support for claim 47 can be found, for example, on page 19, line 29 to page 27, line 8. Claim 48 is supported by the specification on pages 17-19. The new claims do not add any new subject matter.

In sum, claims 36-49 are pending.

THE OBJECTION

The Examiner has objected to claims 41 and 42 under 35 U.S.C. § 132 contending that the April 13, 2001 Amendment introduced "new matter into the disclosure." Specifically, the Examiner alleges that the amendments to claim 41, parts a, b, and c, and claim 42, parts a, b, and c, introduced new matter because "[t]here is no support in the specification for the specific fragments of SEQ ID NO:2 recited in the amended claims." Applicant traverses.

Claims 41 and 42, as originally filed, each depended from claims 19 to 21. Claim 19, in turn, depended from claims 12, 13, 14, 15, or 16. The April 13, 2001 Amendment, therefore, amended claims 41 and 42 to incorporate the subject matter from the non-elected claims from which they formerly depended. Thus, the subject matter of elements a, b, and c of amended claims 41 and 42 was recited in original claims 19, 12, 13 ,14, and 16. Specifically, the preamble to parts a, b, and c was taken from claim 19. The APRIL ligand polypeptide from part a was recited in claim 12. The APRIL ligand polypeptide from part b was recited in claim 13. The APRIL ligand polypeptide from part c was recited in claim 14. The

"soluble ligand Polypeptide" element from parts a, b, and c was recited in claim 16.

35 U.S.C. § 112, 4th ¶ states:

> "Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers. (Emphasis added).

Subject matter found in the original claims as filed cannot form the basis of an objection for new matter. See, M.P.E.P. § 608.04(a). Because claims 41 and 42 are supported by the claims as originally filed, Applicant requests withdrawal of the objection to these claims under 35 U.S.C. § 132.

THE REJECTIONS

35 U.S.C. § 112, 2nd ¶

Claim 37 stands rejected under 35 U.S.C. § 112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim" the invention. Specifically, the Examiner contends that the recitation of "an anti-APRIL receptor antibody" lacks proper antecedent basis. However, claim 37 does not recite "an anti-APRIL receptor antibody."* Therefore, applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 112, 1st ¶

Claims 36 to 42 stand rejected under 35 U.S.C. § 112, ¶1 as "containing subject matter which was not described in the specification in such a way as to enable one

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* It is possible that the Examiner was referring to former claim 38. However, claim 38 has been cancelled herein.

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Specifically, the Examiner alleges that the specification does not teach:

> "a) specific tumor types that produce or overproduce APRIL as a soluble protein or have an APRIL receptor;
> b) a specific agent such as an APRIL variant defined by amino acid sequence which can act as an antagonist *in vivo* at the APRIL receptor or an antibody which recognizes a specific epitope of APRIL or APRIL receptor which would be effective at blocking APRIL from interaction with its receptor when administered *in vivo;* or
> c) the inhibition of malignant cell proliferation *in vivo* following the disruption of the APRIL-receptor interaction."

Applicant traverses each part of the rejection in turn.

(A) Specific Tumor Types and the Presence of APRIL ligand and Receptor

With the teachings of the current invention, the Applicant has significantly contributed to the field of TNF family biology, and specifically APRIL biology, as well as provided important advances in cancer therapeutics discovery.

As the Examiner states, the specification teaches that APRIL is transcribed in normal colon, spleen, pancreas, and prostate tissues as well as in peripheral blood leukocytes. Furthermore, the specification teaches that APRIL is transcribed in cancer cells derived from ovary, prostate, Wilms tumor, colon, endometrium, parathyroid, and pancreas tissues as well as a T-cell lymphoma. Also, the specification teaches that APRIL is expressed in many transformed cell lines, including LNCAP adenocarcinoma, colorectal adenocarcinoma lines SW480 and A549, the Burkitt's lymphoma Raji, melanoma G361, promyelocitic leukemia HL60, Hela Cell S3, chronic myelogenous leukemia K562,and lymphoblastic leukemia Molt-4. See, p. 9, 31-32, and Figure 2. Moreover,

the specification teaches that APRIL transcription is elevated in certain tumor cells (thyroid carcinoma, colon adenocarcinoma, and lymphoma) when compared to normal tissues. See, p. 32.

Importantly, however, by disclosing these facts, the specification makes clear that while APRIL is widely expressed in many normal and tumor tissues as well as transformed cell lines, APRIL expression is dramatically increased in some cancer cells as compared to normal cells. Based on this striking observation by Applicant, a person of skill in the art would realize that APRIL is implicated in cellular proliferation.

A person of skill in the art would further consider the data in Example 2 showing that purified APRIL protein as well as heterologous expression of APRIL cDNA dramatically increases cell proliferation. See Example 2, p. 32-34 and Figures 3-4. Taken together, the Applicant has shown for the first time that 1) APRIL is widely expressed; 2) APRIL is upregulated in certain cancer cells; 3) APRIL is associated with increased cellular proliferation; and 4) APRIL functions at the protein level.

APRIL ligand is a member of the TNF family. The Background of the Invention teaches that TNF family members function by binding to a receptor. See, p. 1-7. Therefore, because Example 2 teaches that APRIL ligand functions at the protein level, a person of skill in the art would recognize that the function must involve the interaction of the APRIL ligand with a receptor.

The Examiner alleges that the specification does not teach that any of the recited tumors produce APRIL as a protein and that those of skill in the art would "recognize that expression of mRNA does not dictate the translation of such mRNA into a polypeptide." In support of this assertion, the Examiner cites Alberts et al., Mol. Biol. of the Cell, 3rd Edition, 1994, p. 465; Shantz and Peg, Int. J. Biochem. Cell

Biol., 1999, 31:107-122; McClean and Hill, Eur. J. Canc., 1993, 29A:2243-2248; and Fu et al., EMBO Journal, 1996, 15:4392-4401. The Examiner asserts that these references stand for the proposition that the "predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation."

However, these references also teach that post-translational regulation is but one step in the process of controlling gene expression. In fact, Alberts teaches that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." See, p. 403, attached hereto as Exhibit A.

Furthermore, implicit in the Examiner's rejection is the idea that significant biological functions of APRIL do not lie at the protein level. Because this is disproved in Example 2, supra, if the skilled artisan were to target APRIL ligand with an antagonist, a likely strategy would be to disrupt the interaction between the APRIL ligand and its receptor. When considered in light of the disclosure and the state of the art, a skilled artisan would have a reasonable expectation of success in practicing the invention as claimed, without undue experimentation. For these reasons, Applicant respectfully requests that this rejection be withdrawn.

The Examiner further alleges that "the specification provides no objective evidence that libraries derived from tumors such as ovary, prostate, Wilms, colon, endometrium, parathyroid,[and] pancreas have a functional APRIL receptor and would be susceptible to the effects of APRIL ligand." The Examiner concludes that one of skill in the art would be subject to undue experimentation without a reasonable expectation of success in order to practice the claimed invention.

In order to satisfy the enablement requirement of 35 U.S.C. § 112, it is not necessary or even possible for applicants to supply an exhaustive list of tumor cell types encompassed by their claims. Enablement does require, however, that the specification teach one of skill in the art to practice the invention as claimed without undue experimentation. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

It is well established that the enablement requirement is met even if routine experimentation is necessary in order to practice the invention. *Id.* at 1402. There, the Court stated, "enablement is not precluded by the necessity for some experimentation such as routine screening. . . . experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not experimentation.'" *Id.* at 1404. Whether experimentation rises to the level of undue is not a simple factual determination but rather requires a weighing of the Forman factors, infra. *Id.* at 1404.

Applicant has demonstrated that purified APRIL protein specifically increases the proliferation of Jurkat T lymphoma cells, the B lymphoma lines Raji and mouse A20 cells, COS, HeLa, and some melanoma cells. See, p. 32-33. A person of skill in the art would understand that APRIL is binding to a receptor on these cells. Based on this understanding, the experimentation required of a person of skill in the art to practice the claimed invention would be routine, not undue.

The relevant inquiry into whether experimentation is undue was described in Ex parte Forman, 230 USPQ 546, 547 (Bd. Pat. Appl. & Inter. 1986):

> "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art.... The test is not merely quantitative, since a considerable amount of experimentation is permissible.... The factors to

> be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims."

With respect to the quantity of experimentation necessary to practice the invention, practitioners in the art of cancer therapeutics discovery expect to perform substantial routine experimentation to identify tumor types that would be responsive to the blocking of APRIL binding to its receptor. The present situation is very similar to the field of monoclonal antibodies considered by the Federal Circuit in *In re Wands*. In re Wands, 8 USPQ2d 1400, (Fed. Cir. 1988). There, the Court held that screening of a large number of negative hybridomas does not render the field unpredictable, because "practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Id* at 1406. Similarly, practitioners in the field of cancer therapeutics discovery are prepared to screen large numbers of tumor types to find those that are responsive to the claimed methods.

Furthermore, and contrary to the Examiner's contention, the present specification provides adequate guidance and working examples for identifying responsive cell types. In particular, the methods disclosed in Example 2 reveal not only cell types that proliferate more rapidly in response to purified APRIL protein, but also cell types that do not. Thus, the specification teaches methods for distinguishing between APRIL-responsive and APRIL non-responsive cell types.

It would also not be feasible for applicants to provide a list of all suitable tumor cell types for use in the present invention. Considering the teachings of the

specification in light of the current state of therapeutics discovery, one of skill in the art has the tools to practice the claimed invention. The Examiner has failed to meet her burden under Forman because it is clear the present application enables the claimed methods of suppressing tumor cell growth and treating cancer. Therefore, the Applicant respectfully requests withdrawal of this rejection.

(B) Specific APRIL Antagonists, Or Antibodies To APRIL Ligand Or APRIL Receptor

In rejecting claims 36, 37, 39 and 40, the Examiner alleges that the specification fails to specifically teach a modified inhibitor form of APRIL effective for blocking the interaction between APRIL and its receptor. The Examiner further alleges that one of skill in the art would be subject to undue experimentation to find fragments or mutants of SEQ ID NO:2 which would be effective in a method of treating cancer because one of skill in the art would not be able to anticipate which specific regions of SEQ ID NO:2 should be deleted or altered.* Applicant traverses.

As explained, supra, In re Wands held that routine experimentation by the skilled artisan does not defeat enablement; one must look to whether it is undue. Further, Ex parte Forman, supra, disclosed eight factors to be considered in determining whether any necessary experimentation is in fact undue; as will be seen, the Examiner has not met her burden under Forman.

Those of skill in the art of cancer therapeutics discovery, having modern molecular biology tools and biochemical screens in hand, are prepared to "cut" proteins of clinical significance into multiple fragments for use in high-throughput biochemical screens. See, e.g., page 26, line 24 to page 27, line 8; p. 30, line 30 to page 31, line 3. Upon

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* The rejection of claim 38 is mooted by its cancellation herein.

reviewing the teachings of the current invention, it would be merely routine experimentation to test different portions of the APRIL-ligand peptide for its ability to suppress the proliferation of appropriate cell lines identified by methods similar to those disclosed in Example 2. And because one of skill in the art would expect to practice routine experimentation, the quantity of experimentation required of the skilled artisan to practice the claimed invention is not undue. For these reasons, withdrawal of this rejection is respectfully requested.

(C) Inhibition Of Malignant Cell Proliferation *In Vivo*

Claims 36-42 stand rejected under 35 U.S.C. § 112 because the Examiner contends the specification does not teach "a specific antibody to APRIL or APRIL receptor that could prevent the binding of free APRIL to its receptor in a manner which would inhibit the growth of a malignant cell." The Examiner also alleges that the specification provides no "objective evidence that an exogenously administered antibody could kinetically compete with APRIL ligand, as APRIL ligand is a potential autocrine growth factor."

Despite the examiner's contentions, the experimentation required to practice the invention is routine, not undue. The issue here is again similar to that of In re Wands, which held that those of skill in the art routinely screen large numbers of negative hybridomas in search of an appropriate monoclonal antibody. Here, a person of skill in the art can, for example, use different fragments from SEQ ID NO:2 for antigens in raising APRIL antiserum or monoclonal antibodies. See, p. 17, line 30 to p. 18, line 21. Conventional techniques could then be used to screen the antisera or antibody preparations to identify which antigens led to antibodies that are useful in the claimed methods. See, e.g., p. 30, line 30 to page 31, line 3.

The Examiner, has not met her burden under Forman in alleging undue experimentation. For example, in applying the "quantity of experimentation" factor, a person of skill in the art would not be subject to undue experimentation for the reasons stated above. Therefore, withdrawal of this rejection is requested.

The Examiner further alleges that because the examples of growth stimulation by APRIL ligand given in the specification all involve cells grown in suspension or monolayer cultures, one cannot extrapolate these results to solid tumors *in situ*. In support of this allegation, the Examiner sites factors such as biological stability, half-life, clearance, tissue penetration, absorption by fluids, cells and tissues, and an inability to formulate a large enough local concentration. The Examiner concludes that the specification provides no evidence that would "allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success." Applicant traverses.

Applicant has provided sufficient evidence and reasoning to show that one of ordinary skill in the art would have been reasonably certain that the claimed methods could be used to suppress the growth of tumor cells *in vivo* that are of a type that were found to be dependent on APRIL using the methods disclosed in Example 2.

The Patent Office has the initial burden of providing evidence that would cause one of skill in the art to reasonably doubt the asserted utility. The Examiner has provided no evidence that the claimed methods would not be effective *in vivo*. The specification teaches that APRIL is widely expressed in many normal and tumor tissues as well as transformed cell lines and that APRIL expression is dramatically increased in some cancer cells as compared to normal cells. A person of skill in the art would understand that APRIL plays an important role in cellular proliferation

and that a promising method of suppressing such cancer cells would be to antagonize the interaction of APRIL with its receptor. Thus, based on Applicant's contribution to the art, a person of skill would be able identify appropriate cancer cell types, identify agents that would inhibit binding of APRIL to its receptor, and move the most promising drug candidates into well-known experimental animal model systems (see, e.g., Burke and Balkwill, Biotherapy 8:229-241 (1996), attached hereto as Exhibit B; Li, Cellular and Molecular Mechanisms of Hormonal Carcinogenesis: Environmental Influences, 447-454, 450 (1996), attached hereto as Exhibit C). Under the patent laws, this is enough.

In view of Example 2 and other references of record, Applicant has met the required burden in establishing that the claimed methods would be effective for suppressing tumor cell proliferation. Thus, a skilled artisan would be able to practice the claimed methods without undue experimentation and with a reasonable expectation of success. Accordingly, the requirements of 35 U.S.C. § 112, first paragraph have been met. Therefore, Applicant respectfully requests withdrawal of these rejections.

CONCLUSIONS

For the foregoing reasons, Applicant believes the claims are in condition for allowance and respectfully requests withdrawal of all objections and rejections.

Respectfully submitted,

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